Remarks

Claim 277 has been amended to correct the repetition of the phrase "selected from the group consisting of." New claims 279-291 have been added and recite aqueous compositions comprising TPFI, ala-TFPI, or TFPI muteins and having other features as described in the specification.

No new matter is added.

Supplemental Information Disclosure Statement, Filed November 16, 2004

Applicants submit herewith a copy of the Supplemental IDS filed November 16, 2004 and copies of the non-entered references for entry and consideration by the Examiner. A copy of the stamped postcard acknowledging that the USPTO received these references on November 16, 2004, is enclosed. Because Applicants have already paid the $180 fee for consideration of these references, no additional fees are believed to be due for this submission. However, if a fee is due, please charge our Deposit Account No. 19-0733.

The Rejection of Claims 71, 73, 111, 114, 115, 118, 127, 128, 270, 271, 273, 275, and 276 under 35 U.S.C. § 102(b)

Claims 71, 73, 111, 114, 115, 118, 127, 128, 270, 271, 273, 275, and 276 are rejected under 35 U.S.C. § 102(b) as being anticipated by Broze, WO93/25230 ("Broze"). Applicants respectfully traverse this rejection.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (emphasis added). Broze does not meet this standard.

First, as the Office Action admits, "Broze does not disclose specifically that the solution comprises arginine." Office Action at page 3, last paragraph. The Office Action however alleges that Woog *et al.*, U.S. Patent No. 5,503,827 ("Woog") can somehow supply the missing disclosure of Broze to render it an anticipatory reference "on the basis of inherency." In doing so, the Office Action ignores the legal standard for anticipation, which requires every claimed element to be described in a single reference. This "single reference" requirement for a rejection under 35 U.S.C. § 102 is the same, whether the rejection is based on express teachings or inherent teachings.

Second, it is black letter law that an inherent anticipation requires that the inherent element necessarily is present in the single reference:

> a prior art reference may anticipate without disclosing a feature of the claimed invention if that characteristic is necessarily present, or inherent, in the single anticipating reference.

Schering Corp. v. Geneva Pharm., Inc., 339 F.3d 1373, 1377 (Fed. Cir. 2003) (emphasis added). Broze does not meet this standard of an inherently anticipating reference. The compositions disclosed in Broze do not necessarily contain "from 200 mM arginine to 300 mM arginine," as recited in claims 71 and 73. Woog does not address Broze and has absolutely no bearing on what is necessarily present in the compositions of Broze. Therefore, Broze does not anticipate claims 71 or 73.

Independent claim 111 and dependent claims 114, 115, 118, 127, and 128 recite an aqueous composition comprising TFPI, ala-TFPI, or a mutein of TFPI or ala-TFPI and one of a group of recited stabilizers, as well as a level of stability (*i.e.*, a half-life at 40°C of the recited polypeptide, as determined using prothrombin time, which is greater than that of a composition comprising TFPI, 150 mM sodium chloride, and 10 mM sodium phosphate and having a pH of

6). The Office Action contends that the TFPI compositions disclosed in Broze inherently have the same stability as the compositions of claims 111, 114, 115, 118, 127, and 128.

As stated above, inherent anticipation requires that the recited stability level is necessarily present in the compositions disclosed in Broze. Again, Broze does not meet this standard. Not all TFPI compositions necessarily have the recited stability level. For example, Figure 9B of the present specification discloses a TFPI composition comprising 150 mM NaCl, 0.005% (w/v) polysorbate-80, and 5 mM phosphate that does not have the recited level of stability. See Figure 9B and the description of this figure on page 7, lines 2-5 of the specification. Table 2, 5th entry, discloses a TFPI composition comprising 150 mM NaCl and 10 mM succinate that does not have the recited level of stability. See page 34 of the specification. Finally, as is clear from Table 2, the TFPI half-life depends on the pH of any particular TFPI/saline composition.

Without further information concerning the solutions disclosed in Broze, there is no disclosure in this reference of a TFPI solution that necessarily has a half-life greater than that of a composition comprising TFPI, 150 mM sodium chloride, and 10 mM sodium phosphate and having a pH of 6. That is, the stability level recited in claims 111, 114, 115, 118, 127, and 128 is <u>not</u> inherent in the TFPI compositions disclosed in Broze. Thus, Broze does not anticipate these claims.

Claims 270, 271, and 273 recite TFPI, ala-human TFPI, or a mutein thereof in a solution having a solubilizer selected from the group consisting of phosphate at a concentration of less than 20 mM or at least 500 mM; acetate at a concentration of at most 20 mM or at least 100 mM; and sulfate at a concentration of at least 120 mM, respectively. Broze does not disclose a TFPI solution having any of solubilizers at the recited concentrations. Therefore, Broze does not anticipate claims 270, 271, or 273.

Claim 275 recites TFPI, ala-human TFPI, or a mutein thereof in a solution having a solubilizer comprising phosphate at a concentration of greater than 20 mM or acetate, wherein the solution does not comprise urea. Broze does not disclose a TFPI solution having these recited features. Therefore, Broze does not anticipate claim 275.

Claim 276 recites TFPI, ala-human TFPI, or a mutein thereof in a solution having a first solubilizer selected from the group consisting of phosphate, sulfate, and acetate, and a second solubilizer selected from the group consisting of sodium chloride at a concentration of at least 1.0 M, magnesium chloride, triphosphate, succinic acid, tartaric acid, malic acid, isocitrate, sodium citrate, phosphate glass, mannitol, sucrose, PEG-400, polysorbate-80, and sorbitol. Broze does not disclose a TFPI solution comprising phosphate, sulfate, or acetate in combination with the any of the recited second solubilizers. Therefore, Broze does not anticipate claim 276.

Broze neither expressly nor inherently discloses all the recited elements of the rejected claims. Thus, Broze does not anticipate the subject matter of claims 71, 73, 111, 114, 115, 118, 127, 128, 270, 271, 273, 275, and 276.

Applicants respectfully request withdrawal of these rejections.

Rejections under 35 U.S.C. § 103(a)

The Office Action maintains many of the same rejections under 35 U.S.C. § 103 as in the prior Office Action dated August 11, 2004. However, the Office Action does not acknowledge Applicants' prior arguments addressing these rejections.

The rejection of claims 73, 85, and 118 over Broze

Claim 73 recites a solution comprising TFPI, ala-TFPI, or a mutein of TFPI or ala-TFPI and "from 200 mM arginine to 300 mM arginine." Claim 85 recites a solution having a pH from

5 to below 7.0 and comprising TFPI, ala-TFPI, or a mutein of TFPI or ala-TFPI and one of a group of recited solubilizers. Claim 118 recites an aqueous composition comprising TFPI, ala-TFPI, or a mutein of TFPI or ala-TFPI polypeptide and having sodium chloride at a concentration of at least 500 mM, a pH from 5 to 10, and a half-life at 40°C of the polypeptide, as determined using prothrombin time, from 20 to about 70 days.

The Office Action asserts,

> It would have been obvious to one of ordinary skill in the art at the time applicants' invention was made to form the LACI compositions of WO'230 having the concentrations and pH's outlined above because WO'230 is not limited to any particular concentrations or pH's (see page 29 line 1 to page 30 line 16) and discloses the need to optimize the concentrations depending upon the patient and mode of administration and because the concentration and pH are art-recognized result-effective variables which are routinely determined and optimized in the pharmaceutical art.

Applicants refer to pages 21-24 of their November 16, 2004 response, providing reasons why Broze contains no suggestion to modify its teachings to arrive at the compositions and solutions of claims 73, 85, or 118. Broze is completely silent regarding TFPI solubility and stability and therefore offers no teaching, suggestion, or motivation for improving these properties. Consequently, there is no teaching, suggestion, or motivation to modify the TFPI compositions in Broze to include (1) "from 200 mM to 300 mM arginine" as recited in claim 73; or (2) any of the solubilizers as recited in amended claim 85.

Likewise, Broze does not teach or suggest an aqueous TFPI composition having pH 5-10 and at least 500 mM sodium chloride concentration, to achieve the level of polypeptide stability as recited in amended claim 118. Absent Applicants' own teachings, one would not know which stabilizers at which concentrations and under what conditions would be effective to obtain the recited stability.

The teachings of daily dosage levels, amounts of active ingredient in a single dose, dosage regimens, preparation forms, and combination therapies at page 29, line 1 to page 30, line 16, of Broze (which the Office Action cites) do not provide this suggestion or otherwise cure the deficiencies of Broze.

Thus, Broze does not render claims 73, 85, or 118 *prima facie* obvious.

The rejection of claims 71, 92, 102, 111, 112, 277, and 278 over Broze in view of Patel

Independent claim 71, as well as claims 92 and 102, recite a solution having a pH from 5 to 10 and comprising, *inter alia*, more than 0.2 mg/ml of TFPI, ala-TFPI, or a mutein of TFPI or ala-TFPI. The solution of claim 71 comprises 200 mM to 300 mM arginine. The solutions of claims 92 and 102 comprise the solubilizer histidine at concentrations "from 5 mM to 20 mM" and "at least 5 mM," respectively.

Independent claim 111 recites an aqueous composition comprising TFPI, ala-TFPI, or a mutein of TFPI or ala-TFPI and a stabilizer selected from the group consisting of polysorbate-80, mannitol, sucrose, chloride, acetate, citrate, phosphate, and mixtures thereof, as well as a level of stability (*i.e.*, a half-life at 40°C of the recited polypeptide, as determined using prothrombin time, which is greater than that of a composition comprising TFPI, 150 mM sodium chloride, and 10 mM sodium phosphate and having a pH of 6). Dependent claim 112, as well as independent claim 277 and its dependent claim 278, recite the same stabilizers and further recite half-life ranges (in days) of the TFPI.

Broze does not disclose the use of arginine or histidine at any concentration. In fact, Broze is silent with respect to the need to improve TFPI solubility or stability. Applicants refer to pages 24 and 25 of their November 16, 2004 response, providing reasons why Patel does not cure the deficiencies of Broze.

Patel itself teaches that the use of histidine as a stabilizer is not "generically applicable to all proteins," as the Office Action asserts. Office Action at page 6, line 3. Patel teaches that histidine affects the stability of different proteins in different ways. Patel explains that, while histidine stabilizes glutamate synthetase, it has the opposite effect in creatine kinase. Col. 1, lines 12-23. "Thus, the art has recognized that different proteins exhibit widely varying inactivation responses." Col. 1, lines 23-27.

Moreover, Patel's Examples 1-4 (which the Office Action cites) illustrate how the stabilizing effect of amino acids on any given protein is highly unpredictable. From the results of Example 2, "Both methionine and histidine extend the storage lifetime of GM-CSF." Col. 4, lines 59-62. The stability of this protein was evaluated over a two-week period at 40°C. Col 4, lines 55-59 and FIG. 2. Using the same storage conditions in Example 4, "Methionine is effective in extending the storage lifetime of IL-4 solutions at high temperatures, but histidine is considerably less effective." Col. 5, lines 12-14. In fact, FIG. 4 shows that the use of histidine actually destabilized IL-4 protein, relative to the control sample.

Therefore, Patel itself shows that while histidine stabilizes the protein GM-CSF, it does not stabilize the protein IL-4. The Office Action's sweeping assertion that "Patel's histidine is generically applicable to all proteins" is therefore incorrect. Patel teaches just the opposite, namely that the effect of histidine is highly protein-specific and therefore highly unpredictable. Patel illustrates these highly unpredictable effects on the proteins IFN, GM-CSF, and IL-4. Moreover, Patel is completely silent regarding the effect of histidine (or any other amino acid) on the stability of TFPI. Patel therefore provides no reasonable expectation that any given amino acid would successfully stabilize a protein completely unrelated to IFN, GM-CSF, or IL-4 (*e.g.*, TFPI).

Because the effect of amino acid stabilizers on any given protein is highly unpredictable, as taught in Patel, one of ordinary skill would not reasonably have expected that either arginine or histidine would stabilize TFPI solutions. The teachings of Patel would not have motivated one of ordinary skill in the art to stabilize solutions comprising TFPI with either arginine or histidine. Furthermore, the motivation to add solubilizers and/or stabilizers is lacking because the primary reference, Broze, does not disclose any need to improve TFPI stability.

The teachings of Broze and Patel, even if *arguendo* combined, do not provide the legally-required elements of a *prima facie* case that claims 71, 92, and 102 are obvious. Also, the teachings of Patel are irrelevant to the patentability of claims 111, 112, 277, and 278, which recite stabilizers other than amino acids.

The rejection of claims 71, 73, 78, 83, 86, 87, 89, 95-99, 111, 116, 119, and 121 over Broze in view of Woog

Independent claim 71 (and its dependent claim 73) and independent claim 78 (and its dependent claims 81-83, 86, 87, 89, and 95-99) recite a solution having a pH from 5 to 10 and comprising more than 0.2 mg/ml of TFPI, ala-TFPI, or a mutein of TFPI or ala-TFPI. The solution of claim 71 also comprises 200 mM to 300 mM arginine. The solution of claim 78 comprises one of a number of recited solubilizers.

Independent claim 111 (and its dependent claims 116, 119, and 121) recite an aqueous composition comprising TFPI, ala-TFPI, or a mutein of TFPI or ala-TFPI and a stabilizer selected from the group consisting of polysorbate-80, mannitol, sucrose, chloride, acetate, citrate, phosphate, and mixtures thereof, as well as a level of stability (*i.e.*, a half-life at 40°C of the recited polypeptide, as determined using prothrombin time, which is greater than that of a

composition comprising TFPI, 150 mM sodium chloride, and 10 mM sodium phosphate and having a pH of 6).

Broze is silent with respect to the need to improve TFPI solubility or stability. Broze does not teach or suggest the use of arginine as recited in claim 71. Broze does not teach or suggest the use of any of the solubilizers recited in claim 78. Nor does Broze teach or suggest the use of any of the stabilizers recited in claim 111 to achieve the recited stability level. Applicants refer to pages 25-27 of their November 16, 2004 response, providing reasons why Woog does not cure the deficiencies of Broze.

Woog generically mentions a vast number of potential preservatives and "auxiliary substances" that can be used in pharmaceutical preparations containing any of a vast number of "human proteins". But Woog does not teach that any particular amino acids are effective as solubilizers, as opposed to stabilizers and buffer substances. Woog does not teach or suggest any concentrations of amino acid solubilizers, much less a concentration of "200 mM arginine to 300 mM arginine," as recited in independent claim 71. Woog does not teach or suggest that any of the solubilizers "sucrose, mannitol, sorbitol, citrate, isocitrate, succinate, malate, polyphosphate, acetate, polysorbate-80, polyethylene glycol, histidine, imidazole, glutamate, glycine, ammonium sulfate, and sodium dodecyl sulfate," as recited in independent claim 78, are effective in solubilizing proteins. Nor does Woog teach or suggest that any of these substances might be used to achieve any particular level of stability, much less a half-life at 40°C, as determined using prothrombin time, of "greater than that of a composition comprising TFPI, 150 mM sodium chloride, and 10 mM sodium phosphate and having a pH of 6," as recited in independent claim 111.

Finally, Woog does not teach or suggest any particular types of proteins (*e.g.*, hydrophobic proteins such as TFPI), out of a vast number of possible "human proteins," which

might benefit from solubilization using any of the recited solubilizers or stabilization using any of the recited stabilizers.

As discussed above, the primary reference Broze does not teach or suggest any need to improve TFPI solubility and/or stability. Thus, one of ordinary skill in the art would not have been motivated to look to Woog for suggestions of how to modify the TFPI preparations of Broze. Even if, *arguendo*, the ordinary skilled artisan had consulted Woog, Woog offers no guidance as to which solubilizers or stabilizers, from a vast number of possibilities, might be effective for any particular protein. Furthermore, Patel teaches and conclusively demonstrates that the effect of amino acid stabilizers on any given protein is highly unpredictable. For these reasons, one of ordinary skill would have had no reasonable expectation of success in combining any of the large number of "auxiliary substances" disclosed in Woog with TFPI solutions.

The teachings of Broze and Woog, even if *arguendo* combined, do not provide the legally-required elements of a *prima facie* case that claims 71, 73, 78, 81-83, 86, 87, 89, and 95-99, 111, 116, 119, and 121 are obvious.

Secondary Considerations of Non-obviousness

Even assuming arguendo that a *prima facie* case of obviousness has been established as to any of the claims presently rejected under 35 U.S.C. § 103(a), Applicants are allowed to provide evidence in rebuttal. *In re Rijckaert*, 9 F.3d 1531, 1532, 28 U.S.P.Q.2d 1955, 1966 (Fed. Cir. 1993), *citing In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). The Supreme Court has held that secondary considerations such as unexpected results and important advantages are relevant as indicia of nonobviousness. *Graham v. John Deere* Co., 383 U.S. 1, 17-18 (1966). Evidence of secondary considerations, where present, must be

considered in a determination of obviousness. *Stratoflex, Inc. v. Aeroquip Corporation,* 713 F.2d 1530, 1538-39 (Fed. Cir. 1983).

Claims 71-77, 263-269, and new claims 281, 282, and 286-291

As discussed above, independent claim 71 (and its dependent claims 72-77) recite a solution comprising, *inter alia*, more than 0.2 mg/ml of TFPI, ala-TFPI, or a mutein of TFPI or ala-TFPI, and 200 mM to 300 mM arginine.

Applicants have discovered that L-arginine unexpectedly increases TFPI solubility by a factor of 100. L-arginine concentrations in the range of 200 to 300 mM strongly influence TFPI solubility. See page 10, lines 6-10 of the specification. Because of this ability to dramatically increase TFPI solubility, the use of L-arginine in a concentration of 200 mM to 300 mM provides an important commercial advantage. L-arginine allows the preparation of pharmaceutically acceptable compositions having TFPI concentrations of more than 0.2 mg/ml. See page 9, lines 24-25 of the specification. These concentrations are sufficient for administration to patients. See page 9, lines 18-20 of the specification. This finding is unexpected because the solubility of TFPI is quite low at the pharmaceutically acceptable pH levels, e.g., pH 5-10. See page 10, line 3 of the specification. In fact, because of the very limited solubility of TFPI, such pharmaceutically acceptable formulations of TFPI are difficult to manufacture. See page 6, lines 3-8 of the specification.

These unexpected results and important advantages of using 200 mM to 300 mM arginine in TFPI solutions are nowhere taught or suggested in the applied references. Therefore, claims 71-77 and 263-269 are patentable over these references. For the same reasons, new claims 281, 282, and 286-291, reciting arginine concentrations from 200 mM to 300 mM, are also patentable over these references.

Claims 78-110 and 270-276

Independent claim 78 recites (and its dependent claims 79-110) recite a solution having a pH from 5 to 10 and comprising more than 0.2 mg/ml of TFPI, ala-TFPI, or a mutein of TFPI or ala-TFPI and one of a group of recited solubilizers. Claims 270-275 recite concentrations and concentration ranges of solubilizers. Claim 276 recites combinations of solubilizers.

Applicants have discovered that the recited solubilizers, concentrations of solubilizers, and combinations of solubilizers provide a surprising and unexpected advantage. The recited solubilizers allow the preparation of pharmaceutically acceptable compositions having TFPI concentrations of more than 0.2 mg/ml. See page 9, lines 24-25 of the specification. These concentrations are sufficient for administration to patients. See page 9, lines 18-20 of the specification. This finding is unexpected because the solubility of TFPI is quite low at the pharmaceutically acceptable pH levels, e.g., pH 5-10. See page 10, line 3 of the specification. Moreover, because of the hydrophobic nature of TFPI, it is surprising that the claimed hydrophilic additives have such a profound solubilizing effect on TFPI. See page 9, lines 13-17 of the specification.

These unexpected results and important advantages of using the recited solubilizers, concentrations of solubilizers, and combinations of solubilizers in TFPI solutions are nowhere taught or suggested in the applied references. Therefore, claims 78-110 and 270-276 are patentable over these references.

Claims 111-128, 277, and 278 and new claims 279-285

Independent claim 111 (and its dependent claims 127 and 128) recite an aqueous composition comprising TFPI, ala-TFPI, or a mutein of TFPI or ala-TFPI and a stabilizer

selected from the group consisting of polysorbate-80, mannitol, sucrose, chloride, acetate, citrate, phosphate, and mixtures thereof, as well as a level of stability (*i.e.*, a half-life at 40°C of the recited polypeptide, as determined using prothrombin time, which is greater than that of a composition comprising TFPI, 150 mM sodium chloride, and 10 mM sodium phosphate and having a pH of 6). Dependent claims 112-126, as well as independent claim 277 and its dependent claim 278-283, recite the same stabilizers and further recite half-life ranges (in days) of the TFPI.

Applicants have discovered that the recited stabilizers have a surprisingly beneficial effect on TFPI stability. For example, the half-life at 40°C of TFPI in isotonic NaCl and 10 mM Na phosphate at pH 6 was found to be only about 11 days, as determined using a prothrombin time assay. However, increasing the NaCl concentration in this composition from 150 mM to 500 mM increases the TFPI half-life more than 6-fold, to about 70 days. See Table 2 and FIG. 11 of the specification. This stability improvement results in practical advantages, in terms of the ability to store TFPI compositions for extended periods.

Such unexpected results and important advantages of using the recited stabilizers in TFPI solutions are nowhere taught or suggested in the applied references. Therefore, claims 111-128, 277, and 278 are patentable over these references. For the same reasons, new claims 279-285, reciting these stabilizers, are also patentable over these references.

In summary, the combination of Broze with Patel and/or Woog neither teaches nor suggests how to overcome the poor solubility of TFPI. Nor do these references teach or suggest how to provide TFPI in pharmaceutically acceptable solutions (at pH 5-10) at acceptable concentrations (more than 0.2 mg/ml) and/or with sufficient stability for practical administration to patients. In contrast to these references, the pending claims recite surprisingly beneficial combinations of features (*i.e.*, concentrations, pH levels, solubilizers, and stabilizers) in TFPI

solutions. These features provide important advantages, especially for clinical indications which may benefit from administration of high doses of TFPI. See page 6, lines 4-6 of the specification.

Because the unexpected properties of the recited TFPI compositions are nowhere taught or suggested in the combination of Broze with Patel and/or Woog, the pending claims are patentable over these references.

The Nonstatutory Double Patenting Rejection of Claims 71, 73, 78, 79, 109, 110, and 263-269

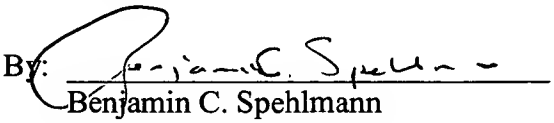
Claims 71, 73, 78, 79, 109, and 110 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 9, 33-37, and 41 of U.S. Patent No. 6,323,326.

Applicants will consider submitting a Terminal Disclaimer when the pending claims are allowable save for the nonstatutory double patenting rejection.

Please continue to direct all correspondence in this application to T. Helen Payne, Esq., Chiron Corporation, Intellectual Property Dept., R440, 4560 Horton Street, Emeryville, CA 94608-2916.

Respectfully submitted,

BANNER & WITCOFF, LTD.

By: 

Benjamin C. Spehlmann
Registration No. 45,649

Date: June 3, 2005

Customer No. 22907

☒ PATENT ☐ DESIGN B&W Ref. 12441.00013 Date: 11/16/04

☐ HAND CARRY Group/Section Bldg Rm

Serial/Patent No.: 09/996588 Atty/Sec: LMH/BCS/mlt

Inventor: Dorin et al. Client: Curis

Title: Formulation, Solubilization, Purification, and Refolding of Tissue Factor Pathway Inhibitor

The following has been received in the U.S. Patent and Trademark Office on the date stamped hereon:

☐ ____ total pp Spec., including : # of Claims ____ # of independent claims ____ ☐ Abstract

☐ Application Data Sheet (ADS): ☐ Initial ☐ Supplemental

☐ Drawings: ☐ Formal ☐ Informal # of distinct sheets ____ Figs: ____

☐ Nonpublication Request

☐ Declaration/Power of Attorney: ☐ Executed ☐ Unexecuted

☐ Assignment w/PTO Cover Sheet

☒ IDS w/PTO 1449 ☒ References ☐ w/Fee

☐ Preliminary Amendment Supplemental

☐ Priority Claim: (Foreign or U.S. Provisional) B&W# ____

Country Appl.# Date

☐ w/Foreign Priority Document(s)

☐ Application: ☐ CIP ☐ Continuation ☐ Divisional

Parent SN: ____ B&W# ____

☐ U.S. Provisional ____ pp Spec/Claims; Cover Sheet

☐ Response to Missing Parts/Requirements dtd ____

☐ Response to Notice to File Corrected Appln. Papers dtd ____

☐ Request for Expedited Foreign Filing License

☐ Request for Corrected ☐ Filing Receipt ☐ Assignment

☐ Response to Restriction/Election Requirement

☐ Sequence Listing. ☐ Diskette ☐ Paper pages ____

☒ Amendment ☒ Response to OA 8/11/04

☒ Petition for Extension of Time until 12/11/04

☐ RCE ☐ w/Ext of Time : OA dtd ____

☐ Request for Approval of Drawing Changes

☐ Notice of Appeal & Fee

☐ Brief ☐ Appeal & Fee ☐ Reply

☐ Request for Oral Hearing

☐ Issue Fee ☐ Pub. Fee ☐ Adv. Pat. Copies #ordered ____

Notice of Allowance dtd ____

☐ Amendment under 37 CFR 1.312

☐ Request for Certificate of Correction

☐ Transmittal ☐ Fee Transmittal w/Auth. to Charge Deposit Acct.

☐ Certificate of Mailing

☐ Check No. ____ for $ ____

☒ Description 2

☐ Polysorbate 80

☐ 1 page paper

(11)

B&W Rev. 01/04